

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements for diphtheria toxoid.

(2) Human. In 1961 to 1962, as part of a combined evaluation of diphtheria and tetanus toxoids, and poliomyelitis vaccine, prison inmates were immunized with various combinations of Parke-Davis diphtheria toxoids (Ref. 4). In most instances, the serologic responses obtained apparently represented booster reactions. Furthermore, it is not clear whether the products used were fluid or adsorbed diphtheria toxoid.

b. Safety--(1) Animal. This product meets Federal requirements for diphtheria toxoid.

(2) Human. There is adequate documentation of the safety in humans of Parke-Davis adsorbed diphtheria toxoids, as contained in the submission.

c. Benefit/risk ratio. This cannot be determined with precision, owing to the absence of satisfactory data documenting the efficacy of this product when used as a primary immunizing agent. However, it is likely that the benefit-to-risk assessment would be satisfactory when the toxoid is used as a booster immunizing agent.

4. Critique. Since this product is not currently on the market, the labeling is badly out-of-date, and requires substantial revision in order to conform with current national recommendations for use of diphtheria toxoids. Furthermore, the statement that children with a negative Schick test do not require diphtheria toxoid is inappropriate, inasmuch

as a Schick negative child may become positive as time goes on, and therefore should have appropriate boosters as recommended in standard immunization schedules.

The Panel finds there is adequate documentation for the safety of this product, for that period of time when this product was previously on the market, as well as adequate documentation of its efficacy in humans when used as a booster immunization. Satisfactory data for the efficacy of adsorbed toxoid in humans, when used for primary immunization, has not been provided.

5. Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product has not been marketed for a number of years in the form for which licensed and consequently there are insufficient data on labeling, safety and effectiveness.

DIPHTHERIA TOXOID, FLUID MANUFACTURED BY

TEXAS DEPARTMENT OF HEALTH RESOURCES

1. Description. This is a fluid diphtheria toxoid which is purified and concentrated by the ammonium sulfate fractionation method. It is diluted in buffered saline and preserved in 1:10,000 thimerosal. It contains 120 Lf of diphtheria toxoid per ml.

2. Labeling--a. Recommended use/indications. The manufacturer recommends this product for use in infants and young children only when there is a contraindication to the administration of preparations of diphtheria toxoid combined with tetanus toxoid and pertussis vaccine. When necessary to administer the preparation to individuals less than 7 years of age, 3 injections of 1.0 ml subcutaneously are recommended at 3 to 4 week intervals. For the primary immunization of individuals greater than 7 years of age it is recommended that adult-type tetanus and diphtheria toxoids be administered. There is no recommendation for reinforcing doses nor is a schedule for primary immunization of individuals 7 years of age or older provided.

b. Contraindications. It is recommended that individuals 7 years of age and older should receive no more than 0.05 ml by injection without testing for sensitivity. Other contraindications are not specified.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. Data directly related to this product are not available.

b. Safety--(1) Animal. This product meets Federal requirements.
(2) Human. No serious reaction has been reported related to the many thousand doses of the product distributed over the 10 year period.

c. Benefit/risk ratio. Although the risk from this preparation is low and the benefit is probably high, in the absence of human data no precise statement can be made regarding primary immunization. However, the benefit-to-risk assessment is satisfactory when the toxoid is used as a booster immunizing agent.

4. Critique. The Panel has a general concern about whether there are present indications for the use of fluid diphtheria toxoid, in the light of greater and more prolonged immunity provided by the adsorbed preparations. Furthermore, although this preparation is presumably highly potent (120 Lf per dose), direct evidence of its superiority to, or comparability with, adsorbed preparations as immunizing agents in humans is not available. Finally, the recommendations for its use are not consonant with those of advisory bodies in the United States.

5. Recommendations. The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued provided that labeling is revised in accordance with the Panel's comments regarding labeling.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the manufacturer's license for this product be maintained for a period not to exceed 3

years, during which time the manufacturer will be expected to provide satisfactory evidence of efficacy in humans under conditions of primary immunization. Labeling should be revised in accordance with the recommendations of this Report.

DIPHTHERIA TOXOID MANUFACTURED BY WYETH LABORATORIES, INC.

The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

DIPHTHERIA TOXOID ADSORBED MANUFACTURED BY

WYETH LABORATORIES, INC.

The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

REFERENCES

- (1) BER VOLUME 2124.
- (2) BER VOLUME 2111.
- (3) BER VOLUME 2053.
- (4) BER VOLUME 2003.

GENERIC STATEMENT ON TETANUS TOXOID

Tetanus is an acute disease of the nervous system caused by infection with the tetanus bacillus, Clostridium tetani, which produces an extremely potent neurotoxin that is lethal to man in miniscule amounts (approximately 7 millionths of a milligram). The tetanus bacillus also produces lesser reactive substances. The disease is of major importance, killing perhaps 1 million people worldwide annually, many of whom are newborns. The tetanus bacillus is probably primarily a resident of the intestinal tract of various animals, but spores are widely distributed in soil and dirt, and when carried into devitalized injured human tissue that is low in oxygen, the spore form of the bacillus can germinate, multiply, liberate toxin and hence cause the disease. The disease can be prevented by immunization with tetanus toxoid. Immunization is indicated for everyone, since natural immunity, if it exists at all, is exceedingly rare in man; not even the disease itself produces immunity in those who recover from it.

Because the morbidity and mortality of tetanus are largely a consequence of the toxin elaborated by the organism, antiserum (antitoxin) prepared by immunizing horses has been used for many decades in the treatment of the disease and for its prevention in exposed susceptible individuals. More recently the use of antitoxin prepared from horse serum has been largely replaced by the use of tetanus immune globulin (TIG) prepared from human serum. This approach to control of the disease is only partially successful because the disease may already

be established by the time of treatment, and toxin that has been adsorbed and fixed to cells is unaffected by antitoxin or TIG. Penicillin or alternative effective antibiotic agents may eradicate the organism, but because they have no effect against toxin, antibiotics are only an adjunct to therapy. For these reasons, passive immunization with antitoxin or immune globulin and therapy with antimicrobial agents have been an unsatisfactory approach to treatment of the disease, and active immunization of humans against the toxin had been employed for many years.

Nature of Product

Tetanus toxoid is a formaldehyde detoxified bacteria-free filtrate of an anaerobic culture of a specially selected strain of Clostridium tetani; sometimes the culture is lysed before filtration to liberate more toxin. Toxin yields are comparable to those obtained with Corynebacterium diphtheriae and indeed the 2 toxins are, as protein molecules, remarkably similar despite the great differences in their pharmacologic action.

Production

Tetanus toxoid is produced with high yields in a simple liquid anaerobic medium, is detoxified with formaldehyde, is partially purified and thus freed of extraneous bacterial proteins, and in final dilution is administered in a dose similar to or slightly less (in terms of flocculation or Lf units) than that for diphtheria toxoid. The medium must contain no substance derived from horses, no known allergens,

and no more than a specified trace of blood grouping substances. Although tetanus toxoid has been widely and successfully used in the plain ("fluid") form, the superiority of aluminum salt-adsorbed tetanus toxoid has been clearly demonstrated, and this form of the toxoid is the most widely used.

Purification of tetanus toxoid is usually accomplished by methanol precipitation, by ammonium sulphate or metaphosphate purification; or less often by ultrafiltration. It is diluted to a concentration that will pass official requirements and a preservative (usually thimerosal) is added. It is subjected to the standard tests for sterility, safety and potency required by the United States regulations.

The antigenicity in man of tetanus toxoid can vary considerably from preparation to preparation; this variation is partly due to variations in the quality and content of toxoid (about 2 to 10 Lf) or of aluminum ion in the adjuvant. The protective level is assumed to be approximately 0.01 unit per ml of tetanus antitoxin toxoid. The geometric mean antibody titer response to various preparations in man after a single dose of either fluid or adsorbed toxoid is extremely variable, from less than 0.001 unit to 0.05 unit. However, with 2 doses of adsorbed toxoid, or 3 doses of fluid toxoid, this variation is greatly reduced and titers usually exceed the protective level.

Use and Contraindications

This product is often used singly as well as in combination with diphtheria toxoid (DT or Td) or with diphtheria toxoid and pertussis

vaccine (DTP). The most commonly used product is DTP, which is routinely recommended for use in children 6 years and under in age; for older children and adults it is recommended that tetanus and diphtheria toxoids (combined) for adult use (Td) be employed for booster purposes. Tetanus toxoid is used singly by physicians who consider that the diphtheria component is either unnecessary, or likely to cause an untoward reaction in the patient. The fluid toxoid is given in 3 doses at least a month apart, with a fourth reinforcing dose, generally about 8 to 12 months later. The adsorbed form is given in 2 doses at least a month apart, with a reinforcing dose as in the case of fluid toxoid. Routine booster injections are recommended at 10 year intervals. In the case of wounds, boosters are recommended if the interval since the last booster is more than 5 years, and in the opinion of some, if the interval is more than 1 year.

In areas where neonatal tetanus is a problem, it can be virtually eliminated by administering either (1) two or more properly spaced doses of adsorbed toxoid to all women of child-bearing age, or (2) two or more doses of adsorbed toxoid during pregnancy, at least a month apart, with the second dose at least 2 and preferably 3 weeks before delivery.

Safety

Problems of adverse reactions to tetanus toxoid have been rare, especially since the elimination, over 30 years ago, of the highly allergenic Witte peptone from the production medium. Most of the local and febrile reactions that are seen appear to be related to more frequent

inoculations than are necessary. In general, however, tetanus toxoid has an almost unique record for safety, no deaths having been associated with the administration of 2.5 million doses in a series reported from Denmark, where a thorough follow-up study was possible.

Manufacturers are required to record reported reactions.

Efficacy

When used as recommended, tetanus toxoid has provided protection to over 95 percent of those inoculated as judged by the induction of serum titers of at least 0.01 antitoxin unit per ml. Indeed, during World War II, only 4 properly immunized United States Army personnel developed tetanus among 2,500,000 persons wounded or injured. Other apparent failures have been reported, but in almost all instances they were associated with incomplete immunization or a false history of immunization.

Special Problems

Continued efforts should be made to establish, for routine lot-to-lot control, the usefulness of the quantitative technique of the evaluation of tetanus toxoids against the International Standards. This technique has been accepted by the European Pharmacopoeia. Direct human testing of any new or altered product should be required until such time as these efforts are completed. The Panel accepts the Bureau of Biologics potency requirements in animals as evidence of adequate immunogenicity for use as a booster in man.

Historically, the antitoxin response to the initial 2 doses of adsorbed toxoid has been excellent. However, recent changes in manufacturing procedures may have resulted in lowering of the immunizing potency of tetanus toxoid in some products; hence there is a need for reevaluating the primary antigenicity of current preparations in man.

Considerable confusion exists concerning the interchangeability of fluid and adsorbed toxoid. However, studies have shown the greater efficacy of adsorbed toxoid, not only in the magnitude but in the

duration of the immune response. This superiority is particularly marked in combined active-passive immunization.

The incidence of reactions, though not of major importance, might be reduced by purification of the toxoid and by eliminating excessive booster doses in highly immunized persons.

Recommendations

There is a need for further studies on the World Health Organization-sponsored quantitative potency test in animals to establish the conditions under which the results are reproducible and to relate these results more closely to those obtained in immunization of man.

Efforts should be encouraged to enhance the immunogenicity of tetanus toxoid without increasing its reactogenicity so that fewer injections are required for primary immunization. Furthermore, it is essential to validate the immunogenicity in man of toxoids in current use that have not already been so tested. An illustrative protocol for such tests has been developed.

It is recommended that the immunogenic superiority of the adsorbed toxoid over the fluid preparation, especially with regard to the duration of protection, be emphasized and be included in labeling of products.

A minimum standard of purity should be established for tetanus toxoid.

Finally, for the tetanus toxoids whose effectiveness can be established by simple blood tests, there must be a resolution of the conflict in public policy between insistence on effectiveness data and constraints

on obtaining such data resulting from the complex issue of informed consent. (See section 2.b. (2) in the Introduction in this Report.)

Basis for Classification

Past experience indicates that all tetanus toxoids which meet the Bureau of Biologics requirements for potency in animal tests have proved effective as boosters in man. Therefore, all currently licensed and marketed products are classified in Category I as regards their use for secondary or booster immunization.

However, quantitative correlation between primary immunogenicity in man and the results of animal protection tests has not been established; therefore direct testing of antitoxin responses in man is required, and should be repeated whenever significant changes in the manufacturing process are made. For those products, therefore, for which such evidence of effectiveness in primary immunization has not been acquired, Category IIIA is recommended.

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(7) VACCINUM TETANICUM ADSORBATUM, supplement to Volume III, pp. 174-178, European Pharmacopoeia 1977, Maisonneuve, S.A., 57 Saint Ruffine, FRANCE.

SPECIFIC PRODUCT REVIEWS

TETANUS TOXOID ADSORBED MANUFACTURED BY BUREAU OF LABORATORIES,

MICHIGAN DEPARTMENT OF PUBLIC HEALTH

1. Description. This preparation comprises tetanus toxoid, adsorbed onto aluminum phosphate, and contains 5 to 10 Lf per 0.5 ml.

2. Labeling--a. Recommended use/indications. This product is recommended for use in the initiation and maintenance of immunity to tetanus in adults. It is specifically recommended that infants and young children be immunized with a combined preparation containing diphtheria toxoid and pertussis vaccine and that adolescent children receive primary immunization with tetanus and diphtheria toxoids of the adult type. The recommended course for primary immunization with this product comprises 2 injections of 0.5 ml intramuscularly 4 to 6 weeks apart, followed by a reinforcing dose 6 to 12 months later. A further reinforcing dose of 0.2 ml every 10 years is advised. The package insert contains no mention of reinforcing doses with injury.

b. Contraindications. Acute respiratory or other infections are given as reasons for deferral of immunization, and a warning about the possibility of an unsatisfactory immune response in individuals receiving immunosuppressive drugs is provided. It is stated that individuals not previously immunized will not be protected by tetanus toxoid at the time of injury and recommends instead that tetanus immune globulin and toxoid, given simultaneously at different sites; be given at the time of injury

followed by later completion of active immunization against tetanus. A warning about rare anaphylactic responses is included.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. As evidence for efficacy, the general literature regarding the effectiveness of tetanus toxoid is cited in the submission to the Panel (Ref. 1). Also, the current paucity of tetanus in the United States and Michigan, as well, is noted. It is concluded that the absence of tetanus in Michigan is due, at least in part, to the millions of doses of tetanus toxoid distributed from this manufacturer in Michigan during the years 1962 through 1972. Serologic evidence of the immunogenicity of this product includes the results of a study of 81 children who received 3 injections of a preparation containing diphtheria toxoid, pertussis vaccine and inactivated poliomyelitis vaccine combined with tetanus toxoid. All children achieved satisfactory titers of tetanus antitoxin. Evidence of efficacy of this preparation for reinforcement of immunity against tetanus is provided in a study of 31 individuals, all with a history of prior tetanus immunization, who were given a single 0.2 ml reinforcing dose. All achieved excellent rises in anti-toxin titers.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. Evidence of human safety is provided by a review of the total number of doses given and the reported reactions over a 10

year period. Among a few million doses there were 4 reactions resembling immediate anaphylactic shock. The remaining reactions were minor and local.

c. Benefit/risk ratio. The benefit-to-risk assessment of this product for primary immunization is probably satisfactory although the lack of data regarding its efficacy in humans as a primary immunizing agent prevents precise evaluation. Its benefit-to-risk assessment for booster immunization is satisfactory.

4. Critique. This extensively used product appears to be quite safe and well-established as efficacious when used for reinforcement of immunity in previously immunized individuals. However, the Panel does not believe that the data relating to the efficacy of tetanus toxoid as a primary immunizing agent when combined with diphtheria toxoid, pertussis vaccine and poliomyelitis vaccine can be extrapolated to substantiate the efficacy of this product when used without such combination.

5. Recommendations. The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which

time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

TETANUS TOXOID, FLUID MANUFACTURED BY CONNAUGHT LABORATORIES, INC.

1. Description. This is a fluid tetanus toxoid containing 12 Lf of toxoid per ml. The toxin is prepared in a casein hydrolysate medium; inactivated by formalin, and diluted in saline containing 15 parts per million of Tween 80.

2. Labeling--a. Recommended use/indications. The recently revised package insert submitted by the manufacturer contains a satisfactory description of the preparation. For primary immunization, 4 subcutaneous injections of 1 ml are recommended, the first 3 being 4 to 8 weeks apart and the fourth dose 6 to 12 months later. Further reinforcing doses are recommended at 5 year intervals. A reinforcing dose with injury is not recommended if less than 1 year has elapsed since the last dose. If the last administration of tetanus toxoid was more than 5 years previously, both a reinforcing dose and tetanus antitoxin are recommended.

b. Contraindications. The manufacturer warns that turbid or cloudy tetanus toxoid should not be used, and a warning about anaphylactic reactions is included. No other contraindication is listed.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. Evidence for efficacy of this product was provided in a 1964-1965 study (Ref. 2) in which 67 children, age 7 to 15 years, were tested for tetanus antibody after a course of 3 injections of Connaught

DT - polio vaccine. Forty-four children had no preimmunization tetanus antibody, and were considered primary responders. All of the 44 sera showed a level of 0.125 antitoxin units per ml or greater 1 month after the third injection. Furthermore, an antibody survey in Ontario, where this toxoid is used almost exclusively for tetanus immunization showed that approximately 98 percent of children less than 18 years of age exhibited satisfactory antibody titers of 0.01 units per ml of serum or more.

The human efficacy data demonstrate somewhat lower titers following immunization than those achieved with adsorbed preparations.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. Of 1,422 injections of tetanus toxoid to employees at Connaught Laboratories, 30 were associated with reactions, all of which were local (Ref. 2). Evidence is also provided by intradermal testing that Sephadex purification of this toxoid markedly reduces local reactions. Only 1 allergic reaction has been reported from several million injections of this toxoid in the last 5 years.

c. Benefit/risk ratio. The benefit-to-risk assessment of this product is very satisfactory.

4. Critique. This fluid tetanus toxoid has been shown to be both safe and efficacious. Although it is questionable whether any fluid toxoid is as immunogenic as adsorbed preparations, both in terms of antibody titers achieved and duration of immunity, when used as recommended its efficacy considerably exceeds the protective threshold. The

package insert deviates from the usual United States recommendations for immunization, particularly in the recommendation that tetanus antitoxin be employed along with a booster if more than 5 years has elapsed since the last dose. The use of tetanus antitoxin under these circumstances is superfluous, assuming that primary immunization has been completed. Further, the package insert contains no comment about the effects of immunosuppressive drugs on the immune response to this product.

5. Recommendations. Although the Panel feels some preference for adsorbed over fluid toxoids, the Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that the package insert should be revised in accordance with currently accepted guidelines. The package insert should also include a recommendation that for the primary immunization of children a combined product containing diphtheria toxoid and pertussis vaccine, as well as tetanus toxoid, is preferred.

TETANUS TOXOID MANUFACTURED BY CUTTER LABORATORIES, INC.

1. Description. Purified tetanus toxoid in sodium chloride, buffered with sodium succinate and containing 1:10,000 thimerosal in a dose of 60 Lf per ml.

2. Labeling--a. Recommended use/indications. This product is used only for hyperimmunization of adults who volunteer to serve as donors in the preparation of human hyperimmune tetanus globulin. It is administered in a dose of 0.5 ml (30 Lf) given by intramuscular or deep subcutaneous route. It is used only by Cutter Laboratories and not marketed. A donor may receive either no more than 3 injections in a single year followed by a single injection the following year, or no more than 1 booster injection per year for 3 years.

b. Contraindications. Any acute respiratory disease or any active infection is reason for deferring an injection. It should be noted here, also, that persons with a history of adverse reactions to tetanus toxoid should be excluded. This is now mentioned under "Adverse Reactions" in the package insert.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. The company summarizes their experience as follows (Ref. 3): Cutter Laboratories, tetanus toxoid, 60 Lf per ml, after total donations of many thousand units of plasma, has been shown to be 90 percent effective in producing adequate plasma tetanus antibody titer (10 international units or more). Also, after many thousand booster

injections and a follow-up of 22,672 donors, tetanus toxoid, 60 Lf per ml has been shown to be safe for hyperimmunization of adult plasma donors for plasma used in the production of tetanus immune globulin (human).

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. Mild side effects were reported (Ref. 3) a total of 10 times following 22,672 booster injections of tetanus toxoid, 30 Lf, giving a low order of incidence: 0.04 percent. Side effects include 5 cases of rash and hives, 3 of mild fever, 1 each of swelling of glands and transient dizziness.

c. Benefit/risk ratio. This product is designed for hyperimmunization of volunteer subjects. Traditional benefit-to-risk assessment are inappropriate considerations. The risk is low; benefit to mankind, high.

4. Critique. This product is used only to produce hyperimmunization of adult tetanus plasma donors. Cutter Laboratories report a very low rate of adverse effects of the relatively high dose of tetanus toxoid (30 Lf) in persons who already have received their basic series of immunization. Prior to the actual booster immunizations each donor reads and signs the tetanus information and donor's consent and release form.

5. Recommendations. The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that the package insert should be revised in accordance with currently accepted guidelines and recommendations of this Report.

TETANUS TOXOID, FLUID MANUFACTURED BY DOW CHEMICAL COMPANY

1. Description. Tetanus toxoid, fluid is a preparation of tetanus toxoid detoxified with formalin, purified and concentrated by alcohol fractionation and containing 8 Lf per 0.5 ml human dose. It is preserved with 0.01 percent thimerosal.

2. Labeling--a. Recommended use/indications. This product is recommended for active immunization against tetanus. The fluid product is recommended primarily for booster use after exposure to tetanus in previously immunized individuals. It is stated that multiple antigen vaccines (i.e., DTP) are preferred for children under 6.

b. Contraindications. Immunization should be deferred if respiratory disease or other active infections exist and in patients under immunosuppressive treatment. Fractional doses are recommended in cerebral injury, asthma, allergies and histories of severe febrile reactions.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. No data on this specific product were provided.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. No specific data on this product were provided. Data from adverse reactions reported to the company and retrieved from their complaint files show no unusual number of reactions. The validity of such data is always open to question, but the rate of reported untoward

reactions is somewhat higher with the fluid product than with the adsorbed product. Most of the reactions were local in nature; allergic or anaphylactoid reactions were noted in a very few cases.

c. Benefit/risk ratio. Assuming that the product can be demonstrated efficacious for primary immunization, the benefit-to-risk assessment would be satisfactory, and is satisfactory for booster immunization.

d. Labeling. Fluid toxoid is recommended for booster doses following injury in the labeling for both fluid and adsorbed toxoids. The more rapid response to fluid toxoid alluded to is of very dubious significance. The recommendation that boosters be given if the previous dose was received more than 1 year previously is obsolete and encourage excessive booster doses. In addition, fluid toxoid in combinations with tetanus immune globulin (TIG) is recommended if more than 10 years have elapsed since the last booster dose. This should be changed to adsorbed toxoid, which is more effective in combination with TIG. The Public Health Service Advisory Committee on Immunization Practices recommendations on wound management should be followed.

The recommendation to defer immunization when polio is present in the community is also obsolete.

4. Critique. In view of the product's ability to meet the potency test in animals specified by minimum requirements, it is adequate for booster immunization use in humans. However, no data are available for the product to demonstrate its efficacy for primary immunization. In

addition, in the opinion of some, there is no real need for the fluid product. The alleged superiority of fluid products for booster doses following injury is of dubious significance.

While specific data on reactions were not provided, safety is not considered a significant issue. Complaint file data indicate no unusual or unexpected problems.

5. Recommendations. The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

TETANUS TOXOID ADSORBED MANUFACTURED BY DOW CHEMICAL COMPANY

1. Description. Tetanus toxoid, adsorbed is an alum-precipitated preparation prepared by the same method as the fluid product but containing 12 to 16 Lf per 0.5 ml human dose versus 8 Lf for the fluid product. The adsorbed product contains 2.5 mgs alum per dose. It is preserved with 0.01 percent thimerosal.

2. Labeling--a. Recommended use/indications. This product is recommended for active immunization against tetanus. The adsorbed product is recommended over the fluid product for primary immunization, although it is stated the fluid product may be used. It is stated the multiple antigen vaccines (i.e., DTP) are preferred for children under 6 years of age.

b. Contraindications. Immunization should be deferred if respiratory disease or other active infections exist and in patients under immunosuppressive treatment. Fractional doses are recommended in cerebral injury, asthma, allergies and histories of severe febrile reactions. Cautions are inserted that aluminum adjuvants may cause fat necrosis or draining cysts if not properly injected.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. No data on this specific product were provided.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. No specific data on this product were provided. Data from adverse reactions reported to the company and retrieved from their

complaint files show no unusual number of reactions. The validity of such data is always open to question, but the rate of reported untoward reactions is somewhat lower with the adsorbed product than with the fluid product. Most of the reactions were local in nature; allergic or anaphylactoid reactions were noted in a very few cases.

c. Benefit/risk ratio. Assuming that the product can be demonstrated efficacious for primary immunization, the benefit-to-risk assessment would be satisfactory, and is satisfactory for booster immunization.

d. Labeling. The package insert states that fluid toxoid is recommended for booster doses following injury. The more rapid response to fluid toxoid alluded to is of very dubious significance. The recommendations that boosters be given if the previous dose was received more than 1 year previously is obsolete and encourage excessive booster doses. In addition, fluid toxoid in combinations with tetanus immune globulin (TIG) is recommended if more than 10 years have elapsed since the last booster dose. This should be changed to adsorbed toxoid, which is more effective in combination with TIG. The Public Health Service Advisory Committee on Immunization Practices recommendations on wound management should be followed.

The recommendation to defer immunization when polio is present in the community is also obsolete.

4. Critique. In view of the product's ability to meet the potency test in animals specified by minimum requirements, it is adequate for booster immunization use in humans. However, no data are available for

the product to demonstrate its efficacy for primary immunization. The alleged superiority of fluid products over adsorbed products for booster doses following injury is of dubious significance.

While specific data on reactions were not provided, safety is not considered to be a significant issue. Complaint file data indicate no unusual or unexpected problems.

5. Recommendations. The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

TETANUS TOXOID, FLUID MANUFACTURED BY ELI LILLY AND COMPANY

1. Description. Each 0.5 ml of this product contains about 7.5 Lf of purified tetanus toxoid in 0.3 M glycine, preserved with 0.01 percent thimerosal.

2. Labeling--a. Recommended use/indications. For active immunization against tetanus, four 0.5 ml doses over 1 year are recommended; emergency boosters and active-passive primary immunization are also listed as indications.

b. Contraindications. Acute respiratory disease or other active infection are contraindications for use. In individuals who have shown sensitivity reactions to previous injections of tetanus toxoid, a small test dose should be given first. Epinephrine should be available to combat severe systemic reactions if they develop.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. No data were presented.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. Few complaints for many million doses are reported and suggest that no major problem exists.

c. Benefit/risk ratio. There is some reason to question the benefit gained from use of this fluid product for primary immunization in light of the limited available data on efficacy. The benefit-to-risk assessment is satisfactory for booster immunization.

4. Critique. This package insert does not point out the general preference for adsorbed rather than fluid toxoid, nor does it indicate the superiority of adsorbed toxoid in active-passive immunization. No data are presented to indicate whether this specific product is effective in man.

5. Recommendations. The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

TETANUS TOXOID ADSORBED MANUFACTURED BY ELI LILLY AND COMPANY

1. Description. A sterile suspension of tetanus toxoid precipitated with aluminum potassium sulfate to a final concentration of 2.25 mg per ml (1.125 mg per dose), and suspended in 0.3 M glycine. About 7.5 Lf of toxoid are present per dose; 0.01 percent thimerosal is added as a preservative. The toxoid is purified by the Pillemer process which is said to remove practically all of the inert proteins.

2. Labeling--a. Recommended use/indications. For active immunization against tetanus, the package insert recommends two 0.5 ml doses 4 to 6 weeks apart and a third dose 1 year later. No special reference is made to the reinforcing dose but normal booster recommendations are up-to-date.

b. Contraindications. Acute respiratory diseases or other active infections are contraindicated. In individuals with preceding history of reactions to tetanus toxoid, small doses should be given. Epinephrine should be at hand.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. No data were presented by the manufacturer. One study by Snyder (Ref. 4) reports rather poor first-dose response to this product, so that some uncertainty exists as to whether it is sufficiently antigenic. It should be noted that this product contained relatively little aluminum ion.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. No controlled observations presented. The complaint file discloses a few complaints for several million doses sold. Most of these were apparently local reactions, pain or febrile reactions. One "systemic" reaction was recorded.

c. Benefit/risk ratio. Provided evidence is furnished to indicate that this product is effective for primary immunization, the benefit-to-risk assessment would be satisfactory and is satisfactory for booster immunization.

4. Critique. The 1 ml label, included with the manufacturer's submission, is almost unreadable. Other labeling supplied by the manufacturer is clear and informative. Comment(s) on the need for careful resuspension of the precipitate appears in the circular for the pre-packaged product but not the standard product. This submission presents less information than is needed on the response of normal individuals to 2 and 3 doses of this product when used as recommended. The labeling should stress the importance of the third dose as part of the primary immunizing series.

5. Recommendations. The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

TETANUS TOXOID, PLAIN MANUFACTURED BY ISTITUTO

SIEROTERAPICO VACCINOGENO TOSCANO "SCLAVO"

1. Description. This product contains 40 to 50 Lf tetanus toxoid per ml.

2. Labeling--a. Recommended use/indications. This preparation is recommended for primary immunization for tetanus. The dose is 0.5 ml intramuscularly or subcutaneously in 3 doses 4 to 6 weeks apart for primary immunization and a fourth dose approximately 1 year later. A booster dose every 10 years is recommended. For wound management, a booster dose is not recommended unless more than 5 years have lapsed since the patient's third or last booster dose.

b. Contraindications. Immunizations are deferred in any acute or active infection and in persons receiving immunodepressants.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. Claims on efficacy are based on published reports cited in the manufacturer's submission to the Panel (Ref. 5) in which the Sclavo product was used and produced satisfactory antitoxin response. However, published data on efficacy when the product is used for primary immunization are lacking. Separate unpublished data showing antibody response when the adsorbed product is used for primary immunization in children, show marginal results, with a relatively large proportion of children not reaching an antitoxin level of 0.01 international units after 2 injections. The product was proven effective as a booster, however.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. The submission states that few complaints of adverse reactions have been reported, without any further analysis of such data.

c. Benefit/risk ratio. The benefit-to-risk assessment would be satisfactory for primary immunization if the product is shown to be effective and is satisfactory for booster immunization.

d. Labeling. Instructions regarding booster doses following wounds could be improved by including the table from the Public Health Service Advisory Committee on Immunization Practices recommendations.

4. Critique. This product meets the United States standards for animal safety and potency and appears to be safe in humans. Additional serologic data establishing its efficacy for use in primary immunization are needed. The efficacy of the product as a booster is established. In the package insert, recommendations regarding booster doses should follow United States guidelines.

Possibility and description of adverse reactions should be mentioned. The manufacturer's data submission does not describe or elaborate on reported adverse reactions.

5. Recommendations. The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

TETANUS TOXOID ADSORBED MANUFACTURED BY ISTITUTO SIEROTERAPICO

VACCINOGENO TOSCANO "SCLAVO"

1. Description. This product contains 10 Lf tetanus toxoid and 2 mg* aluminum hydroxide per 0.5 ml dose. According to the package insert, this product is highly purified, but methods of production and purification are not described.

2. Labeling--a. Recommended use/indications. This preparation is recommended for primary immunization for tetanus. The dose is 0.5 ml intramuscularly in 2 doses 6 to 8 weeks apart for primary immunization and a third dose approximately 1 year later. A booster dose every 10 years is recommended. For wound management, a booster dose is not recommended unless more than 5 years have elapsed since the patient's third or last booster dose.

b. Contraindications. Immunizations are deferred in any acute or active infection and in persons receiving immunodepressants.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. Claims of efficacy are based on published reports cited in the manufacturer's submission to the Panel (Ref. 6) in which the Sclavo product was used in special clinical settings and produced satisfactory antitoxin responses. However, published data on efficacy when the product is used for primary immunization are lacking. Separate unpublished data showing antibody response when the adsorbed tetanus

* The labeling submitted to the advisory Panel is wrong. This product contains 1 mg of $Al(OH)_3$ per dose. It is the Panel's understanding that the labeling has been corrected.

toxoid was used for primary immunization in Italian children, showed marginal results, with a relatively large proportion of children not reaching an antitoxin level of 0.01 international units after 2 injections. The product was proved effective as a booster, however.

Recently (1977) completed studies of this producer's DT and Td among children and adults, conducted in Mexico, show satisfactory antitoxin response for tetanus as well as diphtheria. These studies were included in the manufacturer's license application to the FDA.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. The submission states that few complaints of adverse reactions have been obtained, without any further analysis of such data.

c. Benefit/risk ratio. The benefit-to-risk assessment of this product is satisfactory.

d. Labeling. Instructions regarding booster doses following wounds could be improved by including the table from the Public Health Service Advisory Committee on Immunization Practices recommendations.

4. Critique. This product meets the United States standards for animal safety and potency and appears to be safe in humans. Additional data were provided to the Panel subsequent to the original submission. The data were submitted in support of DT and Td products, but in accordance with the guidelines established by the Panel regarding the extrapolation of data from the use of combined vaccines, there was sufficient information to show that this product is safe and effective. In the package insert, recommendations regarding booster doses should follow the United States guidelines.

The possibility and description of adverse reactions should be included in the package insert. The manufacturer's data submission does not describe or elaborate on reported adverse reactions.

5. Recommendations. The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product. Labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

TETANUS TOXOID MANUFACTURED BY LEDERLE LABORATORIES DIVISION,
AMERICAN CYANAMID CO.

1. Description. This product is a fluid tetanus toxoid prepared from toxin produced by the method of Mueller and Miller, detoxified with formaldehyde, "refined" by the Pillemer method, diluted in phosphate buffer and 0.3 M glycine to a final concentration of 5 Lf per dose, and preserved with 0.01 percent thimerosal.

2. Labeling--a. Recommended use/indications. For active immunization against tetanus, the dose is three 0.5 ml injections intramuscularly at 3 to 4 week intervals and a fourth dose 1 year later. The labeling notes the immunogenic superiority of adsorbed toxoids and the lack of any significant advantage of fluid toxoid as regards speed of booster response. Wound booster recommendations appear to be based on current Public Health Service Advisory Committee on Immunization Practices recommendations.

b. Contraindications. Acute respiratory disease or other active infection; immunosuppressive or cytotoxic therapy.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. Reports of the Investigational New Drug 262 study included in the manufacturer's submission to the Panel (Ref. 7) suggest very poor primary response to preparation D (a fluid toxoid containing 6 Lf per dose but described as "the current commercial product"). Of 10

subjects, 2 were "protected," 4 had minimal antibody levels and 3 had no measurable response. In a second study, only 2 of 6 subjects given this toxoid were primary responders; both of them had only marginal protection at 90 days. The protocol fails to state whether a third injection of the fluid toxoid was given, however, and the antibody responses suggest that it was not given.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. Twenty-eight minor complaints and apparently no major ones in 3 years are recorded, with several million doses distributed. This suggests a low degree of reactivity. Reactions in the studies noted above were nil (in 6 subjects).

c. Benefit/risk ratio. The benefit-to-risk assessment of this product would be satisfactory if the product is shown to be effective for primary immunization and is satisfactory for booster immunization.

4. Critique. The Panel found this to be an exceptionally informative submission, which brings to light the problem of whether or not the responses to "basic" immunization (i.e., 3 doses of fluid or 2 of adsorbed toxin) with recent preparations are less good than had been expected. When "full primary" immunizations (i.e., 4 doses of fluid or 3 doses of adsorbed tetanus toxoid) had been achieved, evidence of immunogenicity was satisfactory. However, this might result in 6 to 12 months of suboptimal protection.

5. Recommendations. The Panel recommends that this product be placed in Category I as regards its use for booster immunization

and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

TETANUS TOXOID ADSORBED MANUFACTURED BY LEDERLE
LABORATORIES DIVISION, AMERICAN CYANAMID CO.

1. Description. Tetanus toxoid is prepared from toxin produced by the method of Mueller and Miller, detoxified with formaldehyde, "refined" by the Pillemer method, diluted in sodium chloride solution and adsorbed with not more than 0.8 mg of aluminum phosphate per dose. The final concentration of toxoid is 5 Lf per dose and 0.01 percent thimerosal is present as a preservative.

2. Labeling--a. Recommended use/indications. For active immunization against tetanus, two 0.5 ml injections intramuscularly at 4 to 6 week intervals and a third dose 1 year later. The labeling notes the immunogenic superiority of adsorbed toxoids and the lack of any significant advantage of fluid toxoid as regards speed of booster response. Wound booster recommendations appear to be based on recent Public Health Service Advisory Committee on Immunization Practices recommendations.

b. Contraindications. Acute respiratory disease or other active infection; immunosuppressive or cytotoxic therapy.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. Reports of the Investigational New Drug 262 study included in the manufacturer's submission to the Panel (Ref. 8) suggest unexpectedly poor primary responses to 2 preparations, 1 with about half the aluminum content, the other with about 4 times the aluminum content

of the standard Lederle Laboratories Division commercial product. With the low adsorbent preparation 2 of 8 primary responders had subprotective levels 30 days after the dual injection. With the higher (maximum permitted) adsorbent content, 2 of 8 primary responders again failed to reach protective levels after 2 doses.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. Fourteen complaints were recorded in 4-1/2 years during which a few million doses of adsorbed toxoid were distributed. Details are lacking but "convulsions" are mentioned in the condensed statement.

c. Benefit/risk ratio. The benefit-to-risk assessment would be satisfactory if the product is shown to be effective for primary immunization, and is satisfactory for booster immunization.

4. Critique. The Panel found this to be an exceptionally informative submission, which brings to light the problem of whether or not the responses to "basic" immunization (i.e., 3 doses of fluid or 2 of adsorbed toxoid) with recent tetanus toxoid preparations are less good than had been expected.

5. Recommendations. The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

TETANUS TOXOID, FLUID MANUFACTURED BY MASSACHUSETTS

PUBLIC HEALTH BIOLOGIC LABORATORIES

1. Description. This is a fluid tetanus toxoid containing 10 Lf per ml of tetanus toxoid, preserved with 1:10,000 thimerosal, and diluted in phosphate buffered saline at a pH of 7.0. The toxoiding agent is formaldehyde, and the purification process is carried out by ammonium sulfate precipitation followed by dialysis against distilled water.

The dose is not specified, for the manufacturer has not produced this material for some years, but desires to retain a license for possible future production.

2. Labeling--a. Recommended use/indications. No labeling was submitted by the producer.

b. Contraindications. No labeling was submitted by the producer.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements. In addition, the efficacy of this product in animals is well documented, due largely to a series of investigations identified in the manufacturer's submission of data to the Panel (Ref. 9) which used products from the Massachusetts Public Health Biologic Laboratories.

(2) Human. The efficacy of this product in humans, measured serologically, is well documented, both when used as a primary immunizing agent, and when used as a tetanus booster. It appears, however, that the adsorbed tetanus toxoid from this same manufacturer induces a

30-fold higher secondary response than does fluid toxoid, on the basis of a comparison of group geometric mean serum antitoxin titers sampled 56 days after an active-passive tetanus immunization study.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. The references cited adequately document the safety of this product.

c. Benefit/risk ratio. The benefit-to-risk assessment of this product is satisfactory.

4. Critique. The Panel has a general concern about the indications for use of a fluid tetanus toxoid, in the light of the documented superiority of adsorbed tetanus toxoid, not only in the magnitude but in the duration of the immune response. Furthermore, the Panel is unable to assess this product adequately in the absence of appropriate labeling, recommendations for use, and contraindications.

5. Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product has not been produced for a number of years and is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness for a contemporary batch of this product.

Were appropriate labeling to be submitted, the Panel would recommend that the manufacturer retain full licensure for this product.

TETANUS TOXOID ADSORBED MANUFACTURED BY MASSACHUSETTS PUBLIC
HEALTH BIOLOGIC LABORATORIES

1. Description. This is an adsorbed tetanus toxoid, containing 10 Lf units per ml of tetanus toxoid, 4 mg per ml of aluminum phosphate, preserved in 1:10,000 thimerosal, and containing sodium chloride and sodium acetate as diluent. The toxoiding agent is formaldehyde, and purification is carried out by ammonium sulfate precipitation and subsequent dialysis against distilled water. The recommended dose, 0.5 ml, contains 5 Lf of tetanus toxoid.

2. Labeling--a. Recommended use/indications. This preparation is recommended for the routine immunization of individuals against tetanus, and for routine and emergency recall injections. For primary immunization, 2 doses of 0.5 ml are recommended at least 4 weeks apart with a reinforcing dose 6 to 12 months later and routine booster doses approximately every 10 years. It is recommended that combination toxoids with diphtheria are preferable for immunization; no mention of DPT appears in the labeling. The recommendations for use appear to be identical to those of the Public Health Service and the Advisory Committee on Immunization Practices.

b. Contraindications. No absolute contraindications are listed. The labeling does state that the material should not be given as elective immunization when the patient has an acute infectious illness.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements. In addition, the efficacy of product in animals is well

documented, due largely to a series of investigations identified in the manufacturers submission of data to the Panel (Ref. 10) which used products prepared by this manufacturer.

(2) Human. The efficacy of this product in humans, measured serologically, is satisfactorily documented, both as regards its effectiveness as a booster and as a primary immunizing agent.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. The safety of this product in humans is adequately documented.

c. Benefit/risk ratio. The benefit-to-risk assessment of this product is satisfactory.

4. Critique. The manufacturer's submission contains satisfactory evidence of both safety and efficacy as well as appropriate and satisfactory labeling.

5. Recommendations. The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product.

TETANUS TOXOID, FLUID MANUFACTURED BY MERCK SHARP &

DOHME, DIVISION OF MERCK & CO., INC.

1. Description. This is a fluid tetanus toxoid containing 20 Lf of toxoid per ml. The toxin is prepared in a special semisynthetic culture medium which is not further described. It is also purified by methods which are not described. The diluting medium is an aqueous solution of 0.3 M glycine and the preservative is thimerosal in a final concentration of 1:10,000.

2. Labeling--a. Recommended use/indications. The labeling states that tetanus toxoid fluid is recommended for all adults and children. Three doses of 0.5 cc (10 Lf) are injected intramuscularly or subcutaneously at an interval of 3 to 4 weeks followed by a reinforcing dose of 0.5 cc after approximately 1 year. A routine booster dose of 0.5 cc is recommended at intervals not greater than 10 years. A booster dose is also recommended immediately upon the occurrence of a wound that potentially may be contaminated unless a booster dose has been given within 1 year.

The recommendation that fluid tetanus toxoid is the preferred preparation for wound booster is of dubious clinical significance. No mention of this is made in the labeling for the adsorbed product. The labeling for the fluid product could be improved by incorporating the table from the Public Health Service Advisory Committee on Immunization Practices recommendations used in the adsorbed product package insert as a convenient booster dose guide for injury.

b. Contraindications. Infants with a history of febrile convulsions should be given fractional doses of tetanus toxoid. Also if unusual reaction occurs following the first injection, the volume of the second injection may have to be reduced. Any febrile respiratory illness or other active infection is reason for delaying use of tetanus toxoid, unless withholding involves greater risk.

The advice that heat sterilized individual needles should be used as a precaution seems outdated in view of current practice. Similarly the caution in performing immunizations during polio epidemics seems unnecessary at the present time because of the rarity of such events.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. No data for this specific product are given. Claims for efficacy are based on references in the submission (Ref. 11) to published reports pertinent to tetanus toxoids in general.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. Claims for safety include reference to literature on safety of tetanus toxoid. Data from complaint files suggest a low rate of reports of adverse reactions, especially to the adsorbed product.

c. Benefit/risk ratio. The benefit-to-risk assessment would be satisfactory if the product is sufficiently immunogenic in man, but because this product has not been marketed for several years, no benefit-to-risk assessment can be made.

4. Critique. This is a product that has not been marketed in this form for several years.

The package insert deviates from the usual United States recommendations for immunization, and is in need of updating.

5. Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

TETANUS TOXOID ADSORBED MANUFACTURED BY MERCK SHARP &
DOHME, DIVISION OF MERCK & CO., INC.

1. Description. This is an adsorbed tetanus toxoid containing 20 Lf of toxoid and 2.0 mgm aluminum sulfate per ml. The toxin is prepared in a special semisynthetic culture medium which is not further described. It is also purified by methods which are not described. The diluting medium is an aqueous solution of 0.3 M glycine and the preservative is thimerosal in a final concentration of 1:10,000.

2. Labeling--a. Recommended use/indications. Tetanus toxoid adsorbed is recommended for primary immunization for tetanus. Two doses (10 Lf) are injected intramuscularly at an interval of 3 to 4 weeks followed by a reinforcing dose of 0.5 cc after approximately 1 year. A routine booster dose of 0.5 cc is recommended at intervals not greater than 10 years. A booster dose is also recommended immediately upon the occurrence of a wound that potentially may be contaminated unless a booster dose has been given within 1 year.

b. Contraindications. Infants with a history of febrile convulsions should be given fractional doses of tetanus toxoid. Also if unusual reactions occur following the first injection, the volume of the second injection may have to be reduced. Any febrile respiratory illness or other active infection is reason for delaying use of tetanus toxoid, unless withholding involves greater risk.

The advice that heat sterilized individual needles should be used as a precaution seems outdated in view of current practice. Similarly

the caution in performing immunizations during polio epidemics seems unnecessary at the present time because of the rarity of such events.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. No data for this specific product were provided with the initial submission. Some additional data were provided by Merck Sharp & Dohme (Ref. 11), but were considered insufficient to demonstrate its effectiveness for primary immunization. Claims for efficacy are based on published reports pertinent to tetanus toxoids in general.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. Claims for safety include reference to literature on safety of tetanus toxoid. Data from complaint files suggest a low rate of reports of adverse reactions.

c. Benefit/risk ratio. The benefit-to-risk assessment would be satisfactory if the product is shown to be effective for primary immunization, and is satisfactory for booster immunization.

4. Critique. In combination with other data available to the Bureau of Biologics about these licensed products and well-known published information on tetanus toxoid, it would seem that safety and efficacy for booster immunization are well established.

The package insert deviates from the usual United States recommendations for immunization, and is in need of updating.

5. Recommendations. The Panel recommends that this product be placed in Category I as regards its use for booster immunization and

that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

TETANUS TOXOID, FLUID MANUFACTURED BY MERRELL-NATIONAL

LABORATORIES, DIVISION OF RICHARDSON-MERRELL INC.

1. Description. This is a fluid tetanus toxoid containing 4 Lf per 0.5 ml, the recommended dose. The preservative is thimerosal, 1:10,000. The culture medium employed is not specified in the material submitted; formaldehyde is used as the toxoiding agent, and subsequent purification includes ammonium sulfate precipitation and subsequent dialysis.

2. Labeling--a. Recommended use/indications. This product is recommended for primary immunization of infants and children. Three injections of 0.5 ml, 3 to 4 weeks apart are recommended, with a fourth dose approximately 1 year later and booster doses every 10 years thereafter. Booster doses with injury are recommended if more than 5 years have elapsed since the last booster. Mention is made in the labeling of the preferability of the adsorbed tetanus toxoid. The recommendations for use appear to be identical to those of the Public Health Service Advisory Committee on Immunization Practices.

b. Contraindications. No absolute contraindications are listed. The labeling suggests that immunization be deferred during the course of any acute illness, and that elective immunization of patients over the age of 6 be deferred during an outbreak of poliomyelitis.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. A substantial body of literature is included in the manufacturer's submission (Ref. 12) which attests to the general efficacy of

tetanus toxoid. None of the evidence supplied, however, relates specifically to tetanus toxoid as produced by Merrell-National Laboratories.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. The submission notes that only 6 reports of adverse reactions were received in a 5 year period during which many million doses were distributed. One of these reactions was anaphylactic in nature, another was associated with upper extremity paralysis and the other 4 were apparently mild reactions.

c. Benefit/risk ratio. The benefit-to-risk assessment of this product for primary immunization cannot be established with certainty, owing to the lack of adequate evidence of efficacy. The benefit-to-risk assessment of this product is satisfactory for booster immunization.

4. Critique. The Panel can accept the evidence for safety of this product, as well as evidence for its efficacy in booster immunization, the latter based on the meeting of current Federal minimum requirements for efficacy in animals. Evidence supporting the efficacy of this product as a primary immunizing agent in humans, however, is lacking.

Furthermore, the Panel has some reservation about the need for fluid tetanus toxoid preparations, in the light of the documented superiority of adsorbed products, both in terms of magnitude and duration of the immune response.

References to the avoidance of immunization during outbreaks of poliomyelitis are probably no longer necessary.

5. Recommendations. The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued.

The Panel recommends that this product be placed in Category IIIA as regards its use in primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. In addition, the labeling, although presently satisfactory, will require periodic revision as indicated in the Generic Statement on Labeling.

TETANUS TOXOID ADSORBED MANUFACTURED BY MERRELL-NATIONAL
LABORATORIES, DIVISION OF RICHARDSON-MERRELL INC.

1. Description. This is a purified tetanus toxoid precipitated with 0.75 percent alum (aluminium potassium sulfate), in an isotonic sodium chloride solution. The toxoiding agent is formaldehyde. The purification process includes ammonium sulfate precipitation and subsequent dialysis. The final product is preserved in 1:10,000 thimerosal. The recommended dose, 0.5 ml, contains 5 Lf units of tetanus toxoid.

2. Labeling--a. Recommended use/indications. This product is recommended for active immunization against tetanus in children and adults. The recommended schedule for primary immunization in both children and adults is 2 injections 4 to 6 weeks apart, followed by a third 0.5 ml dose approximately 1 year after the second injection. A booster dose of 0.5 ml is recommended every 10 years thereafter to maintain adequate protection. If an injury other than a clean minor wound occurs more than 5 years after the last dose, a recall or booster dose is recommended. The superiority of adsorbed tetanus toxoid over fluid tetanus toxoid preparations is indicated in the labeling.

b. Contraindications. No absolute contraindications are listed. The labeling suggests that immunization be deferred during the course of an acute illness, and that elective immunization of patients over the age of 6 months be deferred during an outbreak of poliomyelitis.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. A substantial volume of literature in the submission (Ref. 13) attests to the general efficacy of tetanus toxoid. There are no data on efficacy, however, relating specifically to tetanus toxoid produced by Merrell-National Laboratories.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. The data provided are identical to those submitted for this manufacturer's fluid tetanus toxoid.

c. Benefit/risk ratio. The benefit-to-risk assessment of this product for primary immunization cannot be precisely estimated, owing to the lack of data supporting the efficacy of this product when used as a primary immunizing agent. The benefit-to-risk assessment of this product for booster immunization is satisfactory.

4. Critique. The Panel accepts the evidence for the safety of this product, as well as evidence supporting its efficacy for booster immunization, the latter based on meeting current Federal minimum requirements in animal tests. Specific data in support of the efficacy of this product in humans when used as a primary immunizing agent are lacking.

References to the avoidance of immunization during outbreaks of poliomyelitis are probably no longer necessary.

5. Recommendations. The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued.

The Panel recommends that this product be placed in Category IIIA as regards its use in primary immunization and that the appropriate license be continued for a period not to exceed 3 years, during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. In addition, the labeling, although presently satisfactory, will require periodic revision as indicated in the Generic Statement on Labeling.

TETANUS TOXOID, FLUID MANUFACTURED BY PARKE,
DAVIS AND CO.

1. Description. This toxoid contains 5 Lf tetanus toxoid refined by ultrafiltration per 0.5 ml dose with 0.01 percent thimerosal as preservative.

2. Labeling--a. Recommended use/indications. For active immunization against tetanus. The labeling notes that the American Academy of Pediatrics and the Public Health Service Advisory Committee on Immunization Practices recommended use of adsorbed rather than fluid toxoid (but, nevertheless, the labeling recommends this fluid toxoid). Contrary to general practice, it recommends the use of fluid toxoid with TIG. It fails to note the usual precautions about the reduced efficacy in immunosuppressed individuals.

b. Contraindications. Acute febrile illness is a contraindication. The usual precautions regarding sterile equipment, availability of epinephrine, and avoidance of injection into blood vessels are mentioned.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. No data are presented for this specific product. Some published data (Ref. 13) suggest that the primary immune response to a virtually identical, but experimental fluid preparation is rather short-lived. No data are provided on response after reinforcing inoculation.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. The large number of doses distributed, and the very small number of complaints received, together with the apparently satisfactory experience of MacLennan (Ref. 13), suggest that this product is safe in man.

c. Benefit/risk ratio. There is some reason to question the benefit gained from use of this fluid product, in light of the limited available data on efficacy for primary immunization. The benefit-to-risk assessment for this product when used for booster immunization is satisfactory.

4. Critique. The labeling needs careful revision and updating as noted above. The lack of a buffer in this product is surprising. Available data are insufficient to classify this product when used for primary immunization.

5. Recommendations. The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

TETANUS TOXOID ADSORBED MANUFACTURED BY PARKE,

DAVIS AND CO.

1. Description. Contains 5 Lf tetanus toxoid refined by ultra-filtration per 0.5 ml dose with 0.01 percent thimerosal as preservative. The toxoid is adsorbed on 2.5 mg aluminum phosphate per dose.

2. Labeling--a. Recommended use/indications. For active immunization against tetanus.

b. Contraindications. Acute febrile illness; standard precautions regarding sterile equipment, availability of epinephrine, and avoidance of intravenous injection, are mentioned. The possible reduced efficacy of the product in immunosuppressed individuals is not mentioned.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. No data presented for this specific product. Published studies on a similar experimental product (Ref. 13) indicate a good immune response in man but later studies on a different group (Ref. 14) showed an unexpectedly poor response to the first 2 doses.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. The large number of doses distributed, and the very small number of complaints received, together with the apparently satisfactory experience of MacLennan (Ref. 13), suggest that this product is safe in man.

c. Benefit/risk ratio. Provided the efficacy of this preparation for primary immunization is clearly established the benefit-to-risk

assessment would be satisfactory and is satisfactory for booster immunization.

4. Critique. This is 1 of the few currently used tetanus toxoids for which even limited data for primary immunization in man are available. Six out of 6 patients have shown a vigorous primary response by hemagglutinations titer to 2 doses. However, the data are less than required. Hence further evaluation in man is necessary in order to achieve statistical significance. Post-exposure booster recommendations are now obsolete. The labeling needs some expansion, revision and updating.

5. Recommendations. The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

TETANUS TOXOID ADSORBED MANUFACTURED BY SWISS SERUM AND
VACCINE INSTITUTE BERNE

1. Description. This is an aluminum phosphate adsorbed preparation of tetanus toxoid containing 20 Lf per ml. It contains aluminum phosphate, 2 mg per ml, and is preserved with 0.01 percent thimerosal. The product is said to be purified, but neither the method of purification or detoxification are described.

2. Labeling--a. Recommended use/indications. For active immunization against tetanus. The recommended schedule consists of 2 injections of 0.5 ml each at an interval of 4 weeks and a third injection of 0.5 ml 6 to 12 months later. Booster doses are recommended every 10 years, or in the case of injury, provided the patient has not had an injection within the previous year.

b. Contraindications. This product should not be given during acute illnesses. This product should be administered to children with a history of convulsions only under medical supervision.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. Several published studies are cited in the manufacturer's submission to the Panel (Ref. 15) which show that the product induces an adequate antitoxin response when given as a booster. The data show that these responses are satisfactory when given simultaneously with tetanus immune globulin. The data do not clearly demonstrate the efficacy of the product as a primary immunizing agent.

- b. Safety—(1) Animal. This product meets Federal requirements.
- (2) Human. Reaction rates given for an industrial population studied are low and within expected limits.
- c. Benefit/risk ratio. Assuming that the product is found to be an effective primary immunizing agent, the benefit-to-risk assessment would be satisfactory and is satisfactory for booster immunization.
- d. Labeling. This package insert is in need of revision to bring it up-to-date with current recommendations. A booster dose is recommended in the case of injury if more than 1 year has elapsed since the last injection. This obsolete recommendation invites excessive booster doses; the latest Public Health Service Advisory Committee on Immunization Practices recommendations should be incorporated to clarify this problem and the related need to use tetanus immune globulin in some patients.

The statement concerning administration of the product to children prone to convulsions only "under medical supervision" seems superfluous. The product should always be so administered.

4. Critique. This product has been demonstrated to be adequate for booster immunization. Adequate data are not available to demonstrate its efficacy as a primary immunizing agent.

The safety of the product has been adequately demonstrated, and no unusual frequency of untoward local reactions have been noted.

5. Recommendations. The Panel recommends that this product be placed in Category I as regards its use for booster immunization and

that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

TETANUS TOXOID, FLUID MANUFACTURED BY TEXAS

DEPARTMENT OF HEALTH RESOURCES

1. Description. This is a fluid tetanus toxoid prepared by detoxification of tetanus toxin with formaldehyde (and "heat"), purified by ammonium sulfate fractionation, diluted to 40 Lf per dose, and preserved with 0.01 percent thimerosal.

2. Labeling--a. Recommended use/indications. For active immunization against tetanus. The basic immunization schedule consists of three 1 ml doses at 3 to 4 week intervals with a fourth dose 1 year later. Routine boosters are recommended at 5 year intervals.

b. Contraindications. None listed.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. No human data on antitoxin response to primary or booster immunization are presented. "Periodic blood antitoxin" levels are mentioned but no data were provided. A chart labeled "Tetanus Mortality and Immunization in Texas," submitted (Ref. 16) as evidence of efficacy is unsatisfactory and could be interpreted as suggesting that the decline in incidence slowed down with the introduction of toxoid.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. No controlled studies of reaction rates have been performed. It is stated that no adverse reactions were reported in the past 10 years. The high Lf content of this product is a matter of some concern in this regard.

c. Benefit/risk ratio. Assuming that evidence can be presented that the product is effective for primary immunization, the benefit-to-risk assessment would be satisfactory, and is satisfactory for booster immunization.

d. Labeling. The package insert is in need of professional review and revision to bring it up-to-date with current recommendations. For exposure to risk of tetanus, a booster is recommended if a year has elapsed since the last injection. This obsolete recommendation invites excessive boosters; the latest Public Health Service Advisory Committee on Immunization Practices recommendations should be incorporated to clarify this problem and the related need to use tetanus immune globulin in certain patients. The labeling should put special emphasis on the need for the reinforcing dose at 1 year. Since this is a fluid product, the labeling should also note the published evidence questioning the advisability of using fluid toxoid simultaneously with passively administered tetanus immune globulin.

4. Critique. In view of the product's ability to meet the minimum requirements including the potency test in animals, it is adequate for booster use in humans. However, no data are available to demonstrate its efficacy as a primary immunizing agent.

Two matters are of fundamental concern: a. the Lf content of this product may be excessively high, inviting excessive reactions or possibly even suggesting poor antigenic quality; b. in the opinion of

some, there is no need for a fluid product in view of the superiority of adsorbed products.

5. Recommendations. The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy and rate of adverse reactions of this product when used for primary immunization. Labeling revisions are required.

TETANUS TOXOID, FLUID MANUFACTURED BY WYETH LABORATORIES, INC.

1. Description. This is a fluid preparation of tetanus toxoid containing 5 Lf of tetanus toxoid per 0.5 ml with 1:10,000 thimerosal as a preservative. Sodium chloride is the diluent.

2. Labeling--a. Recommended use/indications. This preparation is recommended for active immunization against tetanus but it is specified that the adsorbed preparation is preferred both for basic immunization and recall doses. Otherwise the recommended use/indications are identical to those of the Public Health Service Advisory Committee on Immunization Practices and the Committee on Infectious Diseases of the American Academy of Pediatrics. For primary immunization, 3 doses at 4 week intervals followed by a reinforcing dose 6 to 12 months later, all of 0.5 ml, are recommended. Routine reinforcing doses at 10 year intervals are recommended, and recommendations for reinforcing doses with injury follow those of public advisory groups. The package insert describes techniques for administration in detail. Fractional doses are recommended for children with cerebral damage, neurological disorders or a history of febrile convulsions. Included are warnings about the transmission of serum hepatitis as a result of improper techniques, the possibility of inadequate immunization of individuals receiving immunosuppressive drugs, the need to determine whether there was an untoward reaction to a prior dose, and the possibility of rare allergic reactions.

b. Contraindications. An acute respiratory or other infection is specified as a contraindication to routine immunization but is not

included as a contraindication to a recall dose following injury. No other specific contraindication is listed.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. No data regarding the efficacy of this specific product in humans are provided.

b. Safety--(1) Animal. Although no data were provided with the submission, the product meets Federal requirements.

(2) Human. No data regarding safety in humans are provided.

c. Benefit/risk ratio. Presumably this product has a satisfactory benefit-to-risk assessment for primary immunization although specific data with which to determine this with precision are not available. The benefit-to-risk assessment is satisfactory for booster immunization.

4. Critique. It is likely that this product is efficacious and quite safe although specific data are not available. The Panel does have some doubts about the need for fluid tetanus toxoid preparations in the light of the apparent superiority of adsorbed products.

5. Recommendations. The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate

license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

TETANUS TOXOID ADSORBED MANUFACTURED BY WYETH LABORATORIES, INC.

1. Description. This is an aluminum phosphate adsorbed tetanus toxoid containing 5 Lf of tetanus toxoid per 0.5 ml. It is preserved in 1:10,000 thimerosal and diluted in saline.

2. Labeling--a. Recommended use/indications. For primary immunization 2 injections of 0.5 ml at 4 week intervals followed by a reinforcing dose 6 to 12 months later are recommended. Routine reinforcing doses are recommended at 10 year intervals. The current recommendations of the Public Health Service Advisory Committee on Immunization Practices and the Committee on Infectious Diseases of the American Academy of Pediatrics are included. However, it is not stated to what populations this specific preparation should be administered. There is no mention of the preferability of combined preparations containing diphtheria toxoids and pertussis vaccine for routine administration.

Techniques for administration are very well described. Fractional doses are recommended for children with cerebral damage, neurological disorders or history of febrile convulsions. Warning about the transmission of serum hepatitis with improper techniques, the possibility of inadequate immunization of individuals on immunosuppressive drugs, the need to determine whether there was an undue reaction to a prior injection, and rare allergic reactions are included.

b. Contraindications. An acute respiratory or other infection is specified as a contraindication except when the reinforcing dose is required following injury. No other absolute contraindication is included.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. A review of the general efficacy of tetanus toxoid, adsorbed, is provided (Ref. 17) but there is no information relating to this specific product.

b. Safety--(1) Animal. Although no data were provided with the submission, this product meets Federal requirements.

(2) Human. The excellent safety record of tetanus toxoid in general is provided in the manufacturer's submission but information relative to this specific product is not included.

c. Benefit/risk ratio. Although this product has been in use for many years and there is no reason to believe that the benefit-to-risk assessment is not satisfactory for primary immunization, no specific data are available. The benefit-to-risk assessment for booster immunization is satisfactory.

4. Critique. From the description of the methods employed in preparing this product and from the statement that required animal testing for efficacy is undertaken, it would seem that this product is both safe and efficacious for booster immunization. However, specific data regarding safety in animals and both safety and efficacy in humans are not provided. The package insert does not specify populations to which this specific product should be given, and preference for combined preparations containing diphtheria toxoid and pertussis vaccine is not expressed.

5. Recommendations. The Panel recommends that this product be placed in Category I as regards its use for booster immunization and the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

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GENERIC STATEMENT

Diphtheria and Tetanus Toxoids (DT) for Pediatric Use

See Generic Statements for monovalent diphtheria and tetanus toxoids.

Description

The combination of diphtheria and tetanus toxoids for pediatric use (DT) is intended for the immunization of children against diphtheria and tetanus under circumstances in which the use of these 2 toxoids combined with pertussis vaccine is undesirable or contraindicated. Current licensed products include both fluid and adsorbed forms of DT.

Production

The manufacturing process basically comprises the production, detoxification, purification and titration of the 2 toxoids independently. By Federal regulation the individual toxoids for the adsorbed forms must be adsorbed prior to combination. Both the tetanus and diphtheria toxoid components must be tested for detoxification prior to combination. After combination, both components must be tested for antigenic potency in animals. Currently there is striking variation among the licensed products in terms of the flocculation titers (Lf) for diphtheria and tetanus toxoids per dose. The ranges of Lf for diphtheria toxoid for the fluid product are 25 to 125 and 7.5 to 25 for the adsorbed product. The Lf range of tetanus toxoid is 5 to 10 for the adsorbed product and 5 to 40 for the fluid product.

Use and Contraindications

This product should be used for primary immunization and for booster doses for children 6 years of age or less in instances in which pertussis immunization is contraindicated. Thus, its major use would be for completion of immunization and for booster doses for children who have responded to the triple combination of diphtheria and tetanus toxoids and pertussis vaccine (DTP) with a significant reaction believed or suspected to be a consequence of the pertussis component. Under such circumstances completion of the primary immunization schedule with adsorbed DT is preferred and should comprise a series of 3 doses (considering the doses of DTP already given as part of the series) with the first 2 given 4 to 8 weeks apart and the third 1 year later. A booster dose of DT should be given at school entry, and subsequent booster doses should be given approximately every 10 years, employing tetanus and diphtheria toxoids combined for adult use (Td). Recommendations for immunization with fluid DT are identical except that the primary series should comprise 4 doses, with the first 3 being given 4 to 8 weeks apart and the fourth a year later. Circumstances may occur, such as outbreaks of diphtheria, in which it would be advantageous for individuals older than 6 years of age to receive a larger amount of diphtheria toxoid than is present in the Td (adult type). Diphtheria and tetanus toxoid may be considered for use under these circumstances.

The only contraindication to the administration of DT is a prior severe hypersensitivity reaction. It is also not recommended for use

in individuals 7 years of age or older. It is advisable not to administer the product during a febrile illness because of possible confusion as to the cause of persistent fever if such should occur.

Individuals receiving corticosteroids or other immunosuppressive drugs may not display an optimum immunologic response; accordingly, if discontinuation of such drugs is anticipated within the immediate future, immunization should be delayed until that time.

Safety

Both components of this combined product are tested for safety in animals and for sterility according to Federal requirements as with the monovalent toxoids.

Efficacy

Minimum requirements specify that the diphtheria toxoid component of the combined product may be tested for potency in guinea pigs either before or after combination, and that the tetanus toxoid component be tested for potency after combination. The Bureau of Biologics releases this combined product based on potency data as determined after combination. Neither the diphtheria nor the tetanus component exerts a significant adjuvant or suppressant effect upon the immunogenicity of the other.

Labeling

The labeling for some of the products is slightly inconsistent with the current recommendations of the Public Health Service Advisory Committee on Immunization Practices and the American Academy of Pediatrics

in that these groups recommend that Td (for adult use) be used for children over 6 years of age. Accordingly, the labeling should be modified for DT (for pediatric use) to recommend that these products be used for children "six years of age and under," rather than for children "under six" as is the case with some of the labeling.

Special Problems

The same problems that exist in terms of the immunogenicity of these toxoids administered in the monovalent form exist in the combined form.

Recommendations

The recommendations made for the individual toxoid components apply to the combined product. It is also recommended that requirements be updated to stipulate testing for potency after combination of the individual products.

Basis for Classification

The basis for classification of this combined product is the same as the basis for classification of the individual toxoid components.

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SPECIFIC PRODUCT REVIEWS

DIPHTHERIA AND TETANUS TOXOIDS ADSORBED MANUFACTURED BY BUREAU
OF LABORATORIES, MICHIGAN DEPARTMENT OF PUBLIC HEALTH

1. Description. This is a combined preparation containing 10 to 20 Lf of diphtheria toxoid and 5 to 10 Lf of tetanus toxoid per 0.5 ml. The toxoids are adsorbed on aluminum phosphate and preserved with 0.01 percent thimerosal.

2. Labeling--a. Recommended use/indications. This product is recommended for the active immunization of children less than 6 years of age. The recommended dosage comprises two 0.5 ml intramuscular injections 4 to 6 weeks apart followed by a reinforcing dose 6 to 12 months later. A further reinforcing dose of 0.5 ml is advised at 5 years of age. The preferability of primary immunization with a tri-valent preparation containing pertussis vaccine is not mentioned. If a dose has not been administered within the previous year, the manufacturer recommends a reinforcing dose of this preparation under any one of 5 circumstances: exposure to diphtheria; injury with risk of contracting tetanus; unusual prevalence or risk of exposure to diphtheria; change of environment; and disasters which result in crowding or dislocation.

b. Contraindications. It is recommended that tetanus and diphtheria toxoids, adsorbed, for adult use be used to produce and maintain active immunity against tetanus and diphtheria in individuals 6 or more years of age because of reactivity of this product. A warning that previously unimmunized individuals will not be protected by this product

in case of exposure to diphtheria or tetanus is included. It is also stated that this preparation is useless in the treatment of diphtheria or tetanus. Any acute respiratory disease or other active infection is considered a contraindication. Deferral of immunization is recommended in individuals receiving short-term immunosuppressive therapy and, in instances of long-term immunosuppressive therapy, an extra dose is recommended 1 or more months after therapy is discontinued.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. The only data available concerning primary immunization of humans related to this product comprise studies with a quadruple vaccine containing pertussis and poliomyelitis vaccines as well (Ref. 1). The adjuvant effect of pertussis vaccine is such that these cannot be accepted as evidence for efficacy of this preparation. There are, however, good data that indicate that this preparation is efficacious when used for reinforcement of immunization in previously immunized children.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. During the 10 years, 1962 to 1972, a few million doses of this preparation were distributed; only 3 reactions, all local, were reported. However, administration of this preparation to institutionalized adults yielded high rates of severe reactions.

c. Benefit/risk ratio. The risk of untoward reactions to this preparation, when used as recommended in children, is negligible.

Efficacy of this preparation when used for booster immunization to diphtheria and tetanus is satisfactory. When used for primary immunization, its efficacy is probably satisfactory but data are not available to permit a definitive conclusion.

4. Critique. This is a widely used adsorbed combined preparation of diphtheria and tetanus toxoids employed for the primary immunization of children and reinforcement of immunity to tetanus and diphtheria in children. Unfortunately conclusive data documenting efficacy as a primary immunizing agent are not available.

5. Recommendations. The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required. The manufacturer should specify the preferability of the trivalent preparation containing diphtheria and tetanus toxoids and pertussis vaccine, adsorbed, for the primary immunization of infants and children.

DIPHTHERIA AND TETANUS TOXOIDS ADSORBED MANUFACTURED

BY DOW CHEMICAL COMPANY

1. Description. This product contains 14 to 17 Lf of diphtheria toxoid, 7 to 10 Lf of tetanus toxoid and not more than 5 mg of potassium alum per dose in 0.3 N glycine, with 1:10,000 thimerosal. The toxoids are fractionated by the alcohol method.

2. Labeling--a. Recommended use/indications. Two intramuscular injections of 0.5 ml each 4 to 6 weeks apart, with a reinforcing dose of 0.5 ml about 1 year later, are recommended for immunization of infants and children under 6 years, when pertussis immunization is not indicated. In older children, its use is permissible if they are first screened by Schick or Moloney tests, but the adult type preparation is preferred. Booster doses are recommended following exposure to diphtheria. The labeling recommends three primary doses for immunization of infants (without explanation).

b. Contraindications. Detailed precautions concerning anaphylactoid reactions are outlined. Immunization should be deferred in the presence of acute infections or immunosuppressive treatment or the presence of a polio outbreak. Fractional doses of single antigens should be used in children with allergies, brain injury, or a history of severe reactions, etc. Various other precautions are included.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. No data on the specific product are presented.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. No data on this specific product are presented.

c. Benefit/risk ratio. In the absence of data, assessment of the effectiveness of this product for primary immunization is not possible. The benefit-to-risk assessment for this product when used for booster immunization is satisfactory.

4. Critique. This is a fairly typical combination of diphtheria and tetanus toxoids for pediatric use. The toxoids are fractionated by a well-established method, but the alum content appears somewhat low. The contraindications given are surprisingly detailed and the recommendations for 3 primary injections in infants are not explained. The data presented on efficacy and safety are derived from published papers on other products, but not on this specific product.

5. Recommendations. The Panel recommends that this product be placed in Category I as regards its use for booster immunization and the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

DIPHTHERIA AND TETANUS TOXOIDS MANUFACTURED BY ELI LILLY AND COMPANY

1. Description. This is an alcohol fractionated toxoid (Pillemer method) and contains 7.5 Lf tetanus toxoid and 25 Lf diphtheria toxoid per 0.5 ml dose. It is preserved with 1:10,000 thimerosal and is diluted in 0.3 molar glycine solution.

2. Labeling--a. Recommended use/indications. For active immunization of children under 6 against diphtheria and/or tetanus in circumstances where use of DTP may be contraindicated. The package circular recommends that three 0.5 ml doses be given subcutaneously at intervals of 4 to 6 weeks for primary immunization and that a reinforcing dose of 0.5 ml be given to children under 6 years of age about one year after the primary series. A booster dose is recommended at the time of entry into school (about 5 years of age).

b. Contraindications. These include active infections, possible exposure to polio, a history of central nervous system damage, or convulsions.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. No data on primary or secondary responses to this specific product were provided.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. No data from detailed studies on this specific product were provided. Data from the manufacturer's complaint files indicated only a low rate of consumer complaints concerning reactions, all of which were mild.

c. Benefit/risk ratio. If the product is demonstrated to have satisfactory immunogenicity in the age group for which recommended, the benefit-to-risk assessment would be satisfactory for primary immunization, and is satisfactory for booster immunization.

d. Labeling. The labeling is slightly inconsistent with the current recommendations of the Public Health Service Advisory Committee on Immunization Practices and the American Academy of Pediatrics in that the latter groups recommend that Td be used for children over 6. Accordingly, the labeling should be modified to recommend that the product be used for children "six and under" (rather than "for children under six").

The labeling should also be modified to reflect the well-documented advantages of the adsorbed product over the fluid product.

4. Critique. This submission is lacking in human data to demonstrate the ability of this product to elicit satisfactory primary or booster antitoxin responses in children of the age group concerned. In conjunction with a study of this type, detailed observations on reactogenicity should also be made.

In addition, the continued need for the fluid product is indeed questionable in view of the superiority of adsorbed toxoids as immunizing agents. Nonetheless, some physicians prefer the fluid product.

5. Recommendations. The Panel recommends that this product be placed in Category I as regards its use for booster immunization and the appropriate license(s) be continued with the stipulation that the

labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

DIPHTHERIA AND TETANUS TOXOIDS ADSORBED MANUFACTURED

BY ELI LILLY AND COMPANY

1. Description. This is an alcohol fractionated toxoid (Pillemer method) and contains 7.5 Lf tetanus toxoid and 25 Lf diphtheria toxoid per 0.5 ml dose. The adsorbed (alum precipitated) product is stated to contain 7.25 mg or less of alum per ml. It is preserved with 1:10,000 thimerosal and is diluted in 0.3 molar glycine solution.

2. Labeling--a. Recommended use/indications. For active immunization of children under 6 against diphtheria and/or tetanus in circumstances where use of DTP may be contraindicated. The package circular recommends that two 0.5 ml doses be given intramuscularly at an interval of 4 to 6 weeks for primary immunization and that a reinforcing dose of 0.5 ml be given one year later. A booster dose of 0.5 ml is recommended at the time of entry into school (about 5 years of age).

b. Contraindications. These include active infections, possible exposure to polio, or a history of central nervous system damage or convulsions.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. No data on primary or secondary responses to this specific product were provided.

b. Safety--(1) Animals. This product meets Federal requirements.

(2) Human. No data from detailed studies on this specific product are provided. Data from the manufacturer's complaint files indicated

only a low rate of consumer complaints concerning reactions, all of which were mild.

c. Benefit/risk ratio. If the product is demonstrated to have satisfactory immunogenicity in the age group for which recommended, the benefit-to-risk assessment would be satisfactory for primary immunization, and is satisfactory for booster immunization.

d. Labeling. The labeling is slightly inconsistent with the current recommendations of the Public Health Service Advisory Committee on Immunization Practices and the American Academy of Pediatrics in that the latter groups recommended that Td be used for children over 6. Accordingly, the labeling should be modified to recommend that the product be used for children "six and under" (rather than "for children under six").

The labeling should also be modified to reflect the well-documented advantages of the adsorbed product over the fluid product.

4. Critique. This submission is lacking in human data to demonstrate the ability of this product to elicit satisfactory primary or booster antitoxins responses in children for the age group concerned. In conjunction with a study of this type, detailed observations on reactogenicity should also be made.

In addition, the continued need for the fluid product is indeed questionable in view of the superiority of adsorbed toxoids as immunizing agents. Nonetheless, some physicians prefer the fluid product.

5. Recommendations. The Panel recommends that this product be placed in Category I as regards its use for booster immunization and the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.